Acute Asthma Exacerbations in Children & Asthma Guideline Updates

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Conflict of Interest

• Nothing to disclose.
Learning Objectives

- Identify clinical features consistent with an asthma exacerbation.
- List 3 conditions in the differential diagnosis of an asthma attack.
- Identify 3 risk factors for ICU admission or death from asthma.
- Describe how recent changes to NHLBI and GINA asthma guidelines impact treatment of asthma.
What is an Asthma Exacerbation?
Definition of an Asthma Exacerbation

- No uniform or consensus definition
- Especially tricky for a first-time wheezer
- Blurry line between “asthma exacerbation” and “poor asthma control”
- A flare-up requiring bronchodilators and steroids??

Salgani 2019
Definition of an Asthma Exacerbation

• GINA:
  “Acute or sub-acute worsening in symptoms and lung function from the patient’s usual status, or in some cases, a patient may present for the first time during an exacerbation.”
  - Shortness of breath
  - Cough
  - Wheezing
  - Chest tightness
  - Decreased lung function
• Some children are “poor perceivers” of symptoms
• Severe exacerbations can happen in children with good baseline asthma control
Triggers of Asthma Exacerbations

- Usually (but not always) exposure to external agent +/- poor adherence to controller
  - Viral respiratory infections
  - Allergens (e.g. pollen, mold, pets)
  - Outdoor air pollution
  - Season changes
  - Thunderstorms
  - Perfumes, cleaners
  - Cigarette smoke

GINA 2019; https://www.beko.co.uk/lifestyle/asthma-proof-your-home
What is actually happening?

Pathophysiology of an Asthma Exacerbation

- Bronchial smooth muscle constriction, airway inflammation and edema, mucus hypersecretion
- Constricted lower airways obstruct flow of air out of the lungs, and patient must work harder to push air out
- Results in tachypnea, wheezing, prolonged expiratory phase
- Eventually, patient tires from increased work of breathing, CO₂ accumulates, and respiratory failure ensues

Image: https://vector.childrenshospital.org/2013/12/the-obesity-asthma-connection-a-link-in-the-innate-immune-system/
Evaluation

• Vitals: Tachycardia from home albuterol use, tachypnea, +/- hypoxemia, +/- fever from concomitant infection

• Physical exam:
  • Wheezing (but beware the “clear chest”)
  • Signs of URI such as rhinorrhea, cough
  • +/- crackles with concurrent infection
  • Prolonged expiratory phase
  • Accessory muscle use, nasal flaring, grunting
  • Breathlessness, can’t speak in full sentences
  • Agitation, somnolence in respiratory failure
Wheezing versus Stridor

**Wheezing**
- INTRA-thoracic source (distal trachea, bronchi, small airways)
- Expiratory if mild
- Biphasic if severe
- Typically high-pitched
- Usually polyphonic (many tones)

**Stridor**
- EXTRA-thoracic source (larynx, vocal cords, subglottis, proximal trachea)
- Inspiratory if mild
- Biphasic if severe
- Typically low-pitched
- Usually monophonic (one tone)

Image: https://www.augustahealth.com/health-focused/amazing-facts-about-your-lungs
Imaging

- CXR is not recommended in straightforward cases
- 2-view chest x-ray is recommended in first-time wheezers to rule out other diagnoses
- Typical findings (not pathognomonic)
  - Hyperinflation, flat diaphragms
  - Peribronchial thickening
  - Streaky interstitial opacities
  - Patchy atelectasis
  - Occasionally right middle lobe infiltrates (RML syndrome)

Image: https://obgynkey.com/childhood-asthma/
“Not all that Wheezes is Asthma”

When to think outside the asthma box?

- First-time wheezer
- Wheezing since birth (congenital airway obstruction, malacia, PCD)
- Upper respiratory symptoms in pre-school child (bronchiolitis)
- Unilateral wheeze in 6 month to 3-year-old (foreign body)
- Hives, angioedema, diarrhea (anaphylaxis)
- Coughing/choking with liquids (chronic aspiration)
- Daily wet cough (protracted bacterial bronchitis, primary ciliary dyskinesia)
- Recurrent pneumonia (immunodeficiency, cystic fibrosis)
Question #1

Which of the following physical exam features is NOT consistent with an asthma exacerbation?

A. Retractions and high-pitched expiratory noises
B. Grunting and frequent cough
C. Prolonged inspiratory phase and stridor
D. Quiet breath sounds
Question #2

Which of the following scenarios is MOST consistent with an asthma exacerbation?

A. 3 month old who attends daycare presenting with cough, profuse rhinorrhea, and crackles and wheezes bilaterally

B. 10 month old presenting with single right-sided high-pitched wheeze, history of choking event earlier today

C. 6 year old with history of recurrent ear infection and daily wet cough since three months of age, presenting with wheezing and worsening cough

D. 5 year old with history of eczema presenting with tachypnea and bilateral polyphonic wheezing
Life-Threatening and Fatal Asthma
Fatal Asthma

- Case studies:
  - Preteen boy from Michigan (Rosenman 2007)
  - 9-year-old girl from London (Guardian 2020)
  - 7-year-old boy from Connecticut (C-hit 2019)
  - 8-year-old boy from Cambridgeshire, England (BBC 2019)
  - 20-year-old male from England (HuffPost 2018)
US Asthma Deaths in Children by Gender (2010-2019)

![Bar chart showing US asthma deaths in children by race from 2010 to 2019. The chart indicates the number of deaths for each year, categorized by race (American Indian or Alaska Native, Asian or Pacific Islander, Black or African American, White). The data is sourced from the CDC 2020 report.](image_url)
Risk Factors for Fatal Asthma

- History of near fatal asthma
- History of intubation and mechanical ventilation
- Hospitalization or ED visit for asthma in past year
- Minority race
- History of psychosocial problems or from socio-economically disadvantaged background
- Currently using or recently stopped oral corticosteroids
- NOT using inhaled corticosteroids at baseline
- Over-use of albuterol (>1 inhaler/month)

GINA 2019; Herrera 2018
Addressing Near-Fatal Asthma

• Early intervention with appropriate therapies
• Break down barriers to care
  • Requires awareness of available resources
• Education, education, education!
• Paradigm shift – asthma is a CHRONIC condition

Herrera 2018; Saglani 2019
For a patient with a severe asthma exacerbation, which of the following is a risk factor for ICU admission or death from asthma?

A. Use of albuterol less than 1 inhaler per month
B. Current or recent use of oral corticosteroids
C. Caucasian race
D. Daily use of inhaled corticosteroids
E. Intermittent use of long-acting beta-agonist (LABA) + inhaled corticosteroid combo
Management of Asthma Exacerbations
Therapies

- Oxygen to keep SpO₂ 94-98%
- Albuterol (short acting beta agonist, SABA)
  - Typically continuous nebulized rather than MDI
  - Beware sensitivity to benzalkonium chloride (BAC)
- Systemic corticosteroids – indicated in all but mildest cases
  - Administer within 30-60 minutes of arrival
  - Oral liquid preferred, equal to IV
  - Prednisolone 2 mg/kg/day (max 40 mg) for 3-7 days, or
dexamethasone 0.6 mg/kg/day (max 16 mg) for 2 days
  - IV needed when vomiting, too dyspneic to swallow, intubated
• Ipratropium (Atrovent) – short-acting anti-cholinergic
  • ED use with albuterol associated with reduced hospitalization rate compared to albuterol alone
• IV magnesium
  • Single dose of 2 g associated with reduced hospitalization rate in children who do not respond to initial treatment
• No clear role in ED/urgent care: HeliOx, LTRA, combo ICS-LABA
# Respiratory Score

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<tr>
<td>&gt;12 yr</td>
<td>≤23</td>
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<td>≥28</td>
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**Inclusion Criteria**
- 1-18 y.o with asthma exacerbation admitted to general medicine service

**Exclusion Criteria**
- Acute illnesses
  - Patients with pneumonia, bronchiolitis, or croup as their primary diagnosis
- Chronic Conditions:
  - Chronic lung disease: e.g., cystic fibrosis, restrictive lung disease, bronchopulmonary dysplasia
  - Cardiac disease requiring baseline medication
  - Airway issues: e.g., vocal cord paralysis, tracheomalacia, tracheostomy dependent
  - Medically complex children
  - Immune disorders
  - Sickle cell anemia

**Retractions**
- None
- Subcostal or intercostal
  - 2 of the following: substernal, intercostal, substernal, OR nasal flaring (infant)
- 3 of the following: substernal, intercostal, substernal, suprasternal, supraclavicular OR nasal flaring / head bobbing (infant)

**Dyspnea**
- 0-2 years
  - Normal feeding, vocalizations and activity
    - 1 of the following: difficulty feeding, decreased vocalization or agitated
    - 2 of the following: difficulty feeding, decreased vocalization or agitated
    - Stops feeding, no vocalization, drowsy or confused
- 2-4 years
  - Normal feeding, vocalizations and play
    - 1 of the following: decreased appetite, increased coughing after play, hyperactivity
    - 2 of the following: decreased appetite, increased coughing after play, hyperactivity
    - Stops eating or drinking, stops playing, OR drowsy and confused
- >4 years
  - Counts to ≥10 in one breath
    - Counts to 7-9 in one breath
    - Counts to 4-6 in one breath
    - Counts to ≤3 in one breath

**Auscultation**
- Normal breathing, no wheezing present
  - End-expiratory wheeze only
  - Expiratory wheeze only [greater than end-expiratory wheeze]
  - Inspiratory and expiratory wheeze OR diminished breath sounds OR both

[https://www.seattlechildrens.org/pdf/asthma-pathway.pdf](https://www.seattlechildrens.org/pdf/asthma-pathway.pdf)
Asthma Pathway

Assess and Score at Triage

**Supplemental O2** should be administered to keep O2 saturation > 90%

1st HOUR (ED)

PHASE 1a

**RS 1-5**
- **Albuterol** MDI 8 puffs
- **Dexamethasone** 0.6 mg/kg x1 (16 mg max)

**RS 6-12**
- **Albuterol** continuous neb 20 mg x1 hr
- **Ipratropium** neb 1.5 mg (0.75 mg for <2 yo)
- **Dexamethasone** 0.6 mg/kg x1 (16 mg max)

Assess and Score at end of 1st hour

2nd HOUR (ED)

PHASE 1b

**RS 1-4**
- If first hour RS 1-5, discharge

**RS 1-4**
- If first hour RS 6-9, observe for 1 hour
- If first hour RS 10-12, observe for 2 hours
- **Albuterol** MDI 8 puffs

**RS 9-12**
- **Albuterol** continuous neb 20 mg/hr
- **Ipratropium** neb 1.5 mg (0.75 mg for <2 yo) if not given
- **Magnesium Sulfate** IV 50 mg/kg x1 (max 2 grams) for age ≥ 2 yo
- Place bed request

Assess and Score at end of 2nd hour

https://www.seattlechildrens.org/pdf/asthma-pathway.pdf
Assess and Score at end of 3rd hour

RS 1-4
- Discharge

RS 5-8
- **Albuterol** MDI 8 puffs
- Give **Ipratropium** neb 1.5 mg (0.75 mg for <2 yo) if not given
- Admit to Phase III

RS 9-12
- ICU Consult for RS 10-12
- **Albuterol** continuous neb 20 mg/hr
- **Magnesium Sulfate** IV 50 mg/kg x 1 (max 2 grams) for age ≥ 2 y.o. if not given
- Admit to Inpatient / ICU
- If undecided on Inpatient or ICU, move on to 4th hour

Assess and Score at end of 4th hour

RS 1-8
- Admit to Inpatient

RS 9-10
- **Albuterol** continuous neb 20 mg/hr x 1 hr

RS 11-12
- Admit to ICU

**Urgent Care Transfer Criteria**
- Score >8 following first hour of nebulized albuterol- send by ALS
- Score 5-8 following 8 puffs of albuterol in second hour- send by ALS
- Signs of clinical deterioration or poor clinical response to therapy

**ED Discharge Criteria**
- RS 1-4 for minimum of 1 hour
  (Patients with an initial RS of 10-12 should be observed for 2 hours prior to discharge)
- Tolerating oral intake
- Adequate family teaching
- Follow-up established

**Discharge Instructions**
- Continue to use albuterol MDI every 4 hours until seen by provider
- Follow up with provider within 24-48 hours (when possible)

For questions concerning this pathway, contact: Asthma@seattlechildrens.org

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Last Updated: April 2018
Next Expected Revision: July 2020
Before Discharge Home

- Education – low hanging fruit!
  - Asthma as a CHRONIC condition
  - Address triggers – SHS, allergens, flu vaccine, etc
  - Spacer +/- mask technique
  - Reinforce daily controller use as prescribed by PCP or pulmonologist
  - Print asthma action plan if available
  - Use pictures when possible
- Follow up with PCP within 1 week to review/provide asthma action plan, review meds, identify and address triggers
- Pulmonary referral for repeated ED visits or hospitalizations
Recent Changes to Asthma Guidelines: Global Initiative for Asthma (GINA)
GINA 2019 Changes: Summary

- Recommend AGAINST use of albuterol alone in mild asthma
- For older children (12 years and up) in mild asthma:
  - As-needed low-dose ICS+formoterol (combo inhaler)
  - As-needed albuterol taken together WITH low-dose ICS
  - Daily low-dose ICS, as-needed albuterol or ICS+formoterol
- For younger children (6-11 years) in mild asthma:
  - As-needed albuterol taken together WITH low-dose ICS
  - Daily low-dose ICS, as-needed albuterol

ICS=inhaled corticosteroid
Rationale for changes

• Moving away from albuterol-only treatment for mild asthma
  • Albuterol only use is an outdated modality (only targets bronchoconstriction, not inflammation)
  • Mild asthma is still associated with adverse outcomes
  • Albuterol overuse has significant adverse effects – downregulation of β-receptors, reduced response, rebound
  • Albuterol overuse associated with negative clinical outcomes (higher risk of death, increased ED presentations)

Dusser, Allergy 2007; Hancox, Respir Med 2000; Stanford, AAAI 2012; Suissa, AJRCCM 1994
Rationale for changes

• No reason to withhold ICS in mild asthma
  • A large body of evidence that low dose ICS substantially reduces risks of severe exacerbations, hospitalizations and death
  • Also improves symptom control and reduces exercise-induced bronchoconstriction

• Need to address the challenge of poor adherence with daily ICS in mild asthmatics with only occasional symptoms

• GINA asked, can PRN use of combo inhalers be the answer?

Suissa, NEJMed 2000; Suissa, Thorax 2002; Pauwels, Lancet 2003; O’Byrne, AJRCCM 2001; Reddel, Lancet 2017
SYGMA Trials

- Compared budesonide daily, budesonide-formoterol PRN, and terbutaline PRN
- Budesonide-formoterol used as needed:
  - Reduced exacerbations compared to PRN SABA
  - Was non-inferior to budesonide BID with PRN SABA, but resulted in 75% lower glucocorticoid dose
- Budesonide-formoterol used as needed was slightly less effective at improving symptom control
- Potential benefits of budesonide-formoterol PRN:
  - Increased acceptability
  - Reduced steroid exposure/side effects
  - Reduced cost
**Adults & adolescents 12+ years**

**Abbreviations:**
- ICS = Inhaled corticosteroid
- SABA = Short acting beta-agonist (albuterol)
- LABA = Long-acting beta-agonist

**ICS-formoterol options in US:**
- Symbicort (budesonide-formoterol) – max 16 puffs/day
- Dulera (mometasone-formoterol) – max 14 puffs/day

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**STEP 1**
As-needed low dose ICS-formoterol *

**STEP 2**
- Daily low dose inhaled corticosteroid (ICS),
- or as-needed low dose ICS-formoterol *
- Leukotriene receptor antagonist (LTRA), or
  low dose ICS taken whenever SABA is taken†

**STEP 3**
Low dose ICS-LABA

**STEP 4**
Medium dose ICS-LABA

**STEP 5**
High dose ICS-LABA

Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R

- Add low dose OCS, but consider side-effects

**Other controller options**
- As-needed low dose ICS-formoterol *

**Other reliever option**
- As-needed low dose ICS-formoterol ‡

**PREFERRED CONTROLLER**
To prevent exacerbations and control symptoms

**PREFERRED RELIEVER**

* Off-label; data only with budesonide-formoterol (bud-form) and BDP-form maintenance and reliever therapy
† Off-label; separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

© Global Initiative for Asthma, www.ginasthma.org
**Personalized asthma management:**
Assess,Adjust,Review response

**Asthma medication options:**
Adjust treatment up and down for individual child’s needs

**Box 3-5B**
**Children 6-11 years**

**STEP 1**
Daily low dose inhaled corticosteroid (ICS)  
(see table of ICS dose ranges for children)

**STEP 2**
Low dose ICS-LABA, or medium dose ICS

**STEP 3**
Low dose ICS+LTRA

**STEP 4**
Medium dose ICS-LABA
Refer for expert advice

**STEP 5**
Refer for phenotypic assessment ± add-on therapy, e.g. anti-IgE

**PREFERRED CONTROLLER**
to prevent exacerbations and control symptoms

**RELIEVER**
As-needed short-acting β₂-agonist (SABA)

* Off-label; separate ICS and SABA inhalers; only one study in children

### Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Child and parent goals

### Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

### Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction
Practical Considerations

- Current evidence is for budesonide-formoterol (Symbicort) only; mometasone-formoterol (Dulera) may be a reasonable alternative.
- Off-label, inconsistent insurance coverage.
- Inhalers may run out prior to 1 month if used PRN.
- Hoping for FDA labeling and drug manufacturing to catch up with guidelines.
- Period of uptake/transition.
- Patient and provider education is key.
Question #4

Which of the following is FALSE regarding the changes to GINA asthma guidelines recommended in 2019?

A. Treatment of mild intermittent asthma with albuterol alone (without inhaled corticosteroid) is strongly recommended.

B. ICS-formoterol is a preferred controller medication for children 12 years and older.

C. ICS-formoterol is a preferred quick-relief medication for children 12 years and older.

D. The use of ICS-formoterol as quick-relief in children under 12 years is not currently recommended.
Recent Changes to Asthma Guidelines: National Heart Lung Blood Institute (NHLBI)
A **focused update** to the 2007 Expert Panel Report 3 (EPR-3) Guidelines for the Diagnosis and Management of Asthma

**Combined effort of the Agency for Healthcare Research and Quality (AHRQ) and National Heart Lung and Blood Institute (NHLBI)**

Developed after GINA 2019 updates and intended to answer separate clinical questions

Evidence is patchy, leading to very narrow recommendations
6 Salient Topics in Asthma Care

- Systematic reviews were published and then used as the basis for the updates on 6 topics:
  - Intermittent Inhaled Corticosteroids
  - Long-Acting Muscarinic Antagonists
  - Indoor Allergen Mitigation
  - Immunotherapy in the Treatment of Allergic Asthma
  - Fractional Exhaled Nitric Oxide Testing
  - Bronchial Thermoplasty
Short Courses of ICS in Young Wheezers

- For children 0-4 years with recurrent wheezing (>3 lifetime episodes of wheeze) not on controller therapy
- Recommendation for a short (7-10 day) course of daily ICS in addition to PRN albuterol
- Initiate at first sign of a cold
- Primary benefit is reduction of exacerbations requiring systemic steroids
Intermittent ICS in Children 12+

- For children 12+ with mild persistent asthma, not already on controller
- Can use ICS along with their albuterol inhaler as needed for acute symptoms
- Compared to daily ICS with PRN albuterol, this strategy is similar in asthma control, QOL, and frequency of asthma exacerbations
- Notice similarities with new GINA guideline (difference here is SABA instead of LABA)
Against Increasing ICS in Children on Controller

- For children 4+ with mild-mod persistent asthma already adherent to ICS controller
- Recommend AGAINST increasing the ICS dose temporarily for acute symptoms
- Does not reduce rate of exacerbations or treatment with systemic steroids
- No improvement in asthma QOL
- Potential for growth suppression
SMART Therapy

- Single Maintenance and Reliever Therapy (SMART)
- For children 4+ at Steps 3 and 4 of pathway
- ICS-formoterol recommended as both controller and reliever
- Contrast with GINA, which recommends this at earlier steps but only in children 12+

![Management of Persistent Asthma in Individuals Ages 5–11 Years](chart)

<table>
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<th>STEP 2</th>
<th>STEP 3</th>
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Long story short...

• Patients are now using Symbicort (budesonide-formoterol) and Dulera (mometasone-formoterol) PRN for exacerbations
• Young wheezers *not* on a controller may get a short course of ICS during a URI, but we should not be *increasing* ICS dose during exacerbations
• As-need albuterol alone (without ICS) is only for the mildest of asthma
  • Otherwise, patient should be getting ICS either as needed with their albuterol or as a daily controller medication
• Guidelines for management of acute exacerbations are unchanged
Knowledge-Check Questions
Question #1

Which of the following physical exam features is NOT consistent with an asthma exacerbation?

A. Retractions and high-pitched expiratory noises
B. Grunting and frequent cough
C. Prolonged inspiratory phase and stridor
D. Quiet breath sounds
Question #2

Which of the following scenarios is MOST consistent with an asthma exacerbation?

A. 3 month old who attends daycare presenting with cough, profuse rhinorrhea, and crackles and wheezes bilaterally

B. 10 month old presenting with single right-sided high-pitched wheeze, history of choking event earlier today

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D. 5 year old with history of eczema presenting with tachypnea and bilateral polyphonic wheezing
Question #3

For a patient with a severe asthma exacerbation, which of the following is a risk factor for ICU admission or death from asthma?

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C. Caucasian race
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C. ICS-formoterol is a preferred quick-relief medication for children 12 years and older.

D. The use of ICS-formoterol as quick-relief in children under 12 years is not currently recommended.
Conclusions
Learning Objectives

• Identify clinical features consistent with an asthma exacerbation.
• List 3 conditions in the differential diagnosis of an asthma attack.
• Identify 3 risk factors for ICU admission or death from asthma.
• Describe how recent changes to NHLBI and GINA asthma guidelines impact treatment of asthma exacerbations.
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